UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE: PROTON-PUMP INHIBITOR PRODUCTS LIABILITY LITIGATION **This Document Relates To:** ***Freddy Bales v. AstraZeneca Pharmaceuticals LP*** **Case No. 2:17-cv-06124**	**MDL No. 2789**

DEFENDANTS' MEMORANDUM OF LAW IN SUPPORT OF MOTION TO EXCLUDE EXPERT TESTIMONY OF GILBERT MOECKEL, M.D., PH.D.

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I. INTRODUCTION

Dr. Gilbert Moeckel, a human pathology expert retained by the Plaintiffs in this MDL, relies upon his analysis of select images of renal tissue slides from animal studies conducted by Takeda[1] as part of the FDA approval process of its proton pump inhibitor (PPI) drug Prevacid® to opine that: (1) the animal studies produced pathological signals that should have alerted Takeda to dose-related kidney injuries that would have been relevant in humans, and (2) Takeda failed to reasonably investigate those risk factors. In order to reach these opinions, Dr. Moeckel criticized the initial findings of rat studies conducted in the 1990s, which attributed the renal lesions found in both control animals (*i.e.*, those not exposed to Prevacid®) and treated animals to an age-related, spontaneous condition unique to rats, Chronic Progressive Nephropathy ("CPN"). Dr. Moeckel erroneously argues that instead, Takeda should have investigated these renal lesions as a drug-induced reaction.

Preliminarily, Dr. Moeckel's opinions, all of which appear to link PPIs to drug-induced acute kidney injuries, do not fit the facts of this case, where Plaintiff Freddy Bales alleges a single kidney injury: chronic kidney disease ("CKD"), not an acute kidney injury or the rat-specific CPN. Based upon his review of animal renal tissue, Dr. Moeckel does not opine that Prevacid® use causes CKD in humans, nor do any of Plaintiffs' other experts rely on his analysis to reach that conclusion.

Further, Dr. Moeckel's opinions exceed the scope of his qualifications. He has admitted that: (1) he is not a veterinary pathologist or a toxicologist; and (2) that, in his experience as a

[1]The Takeda Defendants ("Takeda" collectively) consist of Defendants Takeda Pharmaceuticals U.S.A., Inc., Takeda Pharmaceuticals America, Inc., Takeda Development Center Americas, Inc. f/k/a Takeda Global Research & Development Center, Inc., and Takeda Pharmaceutical Company Limited.

pathologist, he has *never* seen CPN, even in the Takeda images he reviewed and even though he acknowledged that CPN exists. He thus lacks the qualifications to offer reliable scientific opinions analogizing animal kidney conditions to the human kidney.

Finally, Dr. Moeckel's testimony belied any semblance of a reliable, scientific methodology. He repeatedly admitted ignorance of—or outright disagreement with—published literature concerning the idiosyncrasies of rat kidneys and the parameters of CPN, a condition he admittedly has never seen. Pressed to explain his disagreement with published literature, Dr. Moeckel expressed concerns about letting drug manufacturers "off the hook." Ex. A, 7-7-2021 Dep. of Gilbert Moeckel, M.D., Ph.D. ("Moeckel Dep. vol. I") at 120:8–18. Yet, he failed to provide any scientific basis for these criticisms.

Further demonstrating the conclusion-driven nature of his opinions, Dr. Moeckel's analysis of Takeda's animal studies suffered from the following glaring methodological flaws: (1) lack of written notes about the thousands of slides he purportedly reviewed; (2) lack of a grading system to differentiate the severity of certain cellular phenomena; (3) lack of cross-references to the original study findings; and (4) lack of methodology for adjusting / comparing human dosage levels to the rat dosage levels in the animal studies. Far from relying on sufficient facts and data, Dr. Moeckel simply selected a handful of slides that he knew were not in the animal studies' control group, made "mental notes," and used them in his report, discarding the thousands of other slides that did not support his conclusion.

For all of these reasons, Dr. Moeckel's opinions should be excluded in their entirety under Federal Rule of Evidence 702 and the *Daubert* standard.

II. BACKGROUND

Dr. Moeckel, a board-certified pathologist who specializes in assessments of *human* kidney tissue, offers a variety of pathology-related opinions from his review of the images of *rat*, *mouse*, and *dog* kidney tissue from Takeda's preclinical studies. Specifically, he opines that:

- Takeda animal studies showed nephrotoxic signals of renal tubular (and other) renal injuries of greater severity with increasing dose and duration in test animals compared with controls;
- Takeda failed to fully assess the nephrotoxic potential of its PPI in the nonclinical setting despite the aforesaid findings;
- There are biologically plausible mechanisms by which PPIs induce tubular injury in the kidneys of test animals that are relevant in humans; and
- By failing to investigate the tubular renal signals seen in PPI-dosed animals, Takeda allowed a drug with subclinical, nephrotoxic potential to enter the market for popular use in humans.

Ex. B, Report of Dr. Gilbert Moeckel ("Moeckel Report") at 4 ("Summary of Opinions"). According to Dr. Moeckel, in his review of the preclinical study images of renal tissue, he "always saw an acute component" in the renal lesions "in the drugged animals, which in my opinion does not fit in the definition of chronic progressive nephropathy." Ex. C, 7-8-2021 Dep. of Gilbert Moeckel, M.D., Ph.D. ("Moeckel Dep. vol. II") at 412:4–15.

Dr. Moeckel claims to have reviewed more than 7,000 images of kidney tissue from 15 Takeda preclinical studies, along with the reports related to those studies. Moeckel Report at 6. Whereas the original reviewing pathologists for the preclinical study reports "typically diagnosed [kidney] lesions as species-specific, age-related changes that are irrelevant in humans," Dr. Moeckel claims to have "identified lesions in the kidney that occurred in greater numbers and in greater degrees of severity in the dosed animals versus the controls." *Id.* In other words, Dr. Moeckel believes that certain lesions he observed in a handful of dosed-group animals should have

alerted the reviewing pathologist of "study-drug induced changes that warranted further investigation," instead of a chronic, rat-specific kidney condition. *Id.* at 14.

Summarizing his findings, Dr. Moeckel claims to have found "kidney findings in several species of dosed animals," which "mostly consisted of acute tubular injury, inflammatory interstitial infiltrate, tubular cast formation and glomerular amyloid deposits," as well as "extensive green, intratubular crystal deposits." *Id.* at 35. Going one step further, he claims "[t]hese findings are consistent with drug-induced kidney injury pathology in human kidney biopsies." *Id.* at 36.

III. LAW AND ARGUMENT

A. Legal Standard

Under the Federal Rule of Evidence 702 standard for expert witnesses, one "who is qualified as an expert by knowledge, skill, experience, training, or education may testify in the form of an opinion or otherwise if:

> (a) the expert's scientific, technical, or other specialized knowledge will help the trier of fact to understand the evidence or to determine a fact in issue;
>
> (b) the testimony is based on sufficient facts or data;
>
> (c) the testimony is the product of reliable principles and methods; and
>
> (d) the expert has reliably applied the principles and methods to the facts of the case.

Fed. R. Evid. 702.

Accordingly, before courts may admit expert opinions under Rule 702, the proponent of the evidence must establish that the "expert testimony is sufficiently relevant and reliable to be admissible." *Oddi v. Ford Motor Co.*, 234 F.3d 136, 144 (3d Cir. 2000). This not only requires the expert to establish that his opinions will "help the trier of fact . . . to determine a fact in issue," but

also that the expert's testimony is "based on sufficient facts or data" and "the product of reliable principles and methods." Fed. R. Evid. 702.

As a threshold matter, the expert must have sufficient qualifications—*i.e.*, "specialized expertise"—to opine on the relevant topic. *Schneider ex rel. Estate of Schneider v. Fried*, 320 F.3d 396, 404 (3d Cir.2003). Further, the expert's testimony must "fit" the issues in the case by providing "a valid scientific connection to the pertinent inquiry" in the case. *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 591 (stating that the district court's "gatekeeping role" requires ensuring that the expert testimony "is relevant to the task at hand"). The "fit" between data and expert opinion is a key component of admissibility. *In re TMI Litig.*, 193 F.3d 613, 670 (3d Cir. 1999) (citing *Daubert*, 509 U.S. at 590). Admissibility thus "depends, in part, on a connection between the expert opinion offered and the particular disputed factual issues in the case." *Id.* This requirement "is one of relevance and expert evidence which does not relate to an issue in the case is not helpful." *Id.*

Under Rule 702, the proponent of expert testimony must establish that the expert's testimony is "reliable," which requires in turn "that it must be 'scientific,' meaning grounded in the methods and procedures of science, and must constitute 'knowledge,' meaning something more than speculative belief or unsupported speculation." *Soldo v. Sandoz Pharm. Corp.*, 244 F. Supp. 2d 434, 527 (W.D. Pa. 2003). This Court's "gatekeeper" role thus requires it "to make certain that an expert, whether basing testimony upon professional studies or personal experience, employs in the courtroom the practice of an expert in the relevant field." *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 152 (1999). When an expert's testimony "relies in part on his own *ipse dixit*, rather than on something more readily verifiable . . . it is open to attack." *In re TMI Litig.*, 193 F.3d at 687 ("[S]omething doesn't become 'scientific knowledge' just because it's uttered by a scientist; nor

can an expert's self-serving assertion that his conclusions were 'derived by the scientific method' be deemed conclusive.")

B. Dr. Moeckel's Opinions Do Not "Fit" the Facts of this Case.

Preliminarily, Dr. Moeckel's animal-study opinions, which repeatedly dispute the presence of CPN in rat kidneys, do not fit the facts of this case. The Plaintiff in this case alleges that his use of Prevacid® and another PPI caused a CKD. *See* Doc. 42, 2nd Am. Short Form Compl. ¶ 11.[2] How, then, does denying the existence of a spontaneous, age-related, rat-specific kidney disease by pointing to allegedly overlooked acute renal pathology support such a claim?

Nothing in Dr. Moeckel's report or testimony suggests that he intends to offer any opinion that the use of PPIs causes CKD in humans. Nor do any other Plaintiff's experts rely on Dr. Moeckel's review of images from animal studies to conclude that the use of PPIs causes CKD in humans. Instead, the principal thrust of Dr. Moeckel's animal-study opinions has been that lesions appearing in those images reflected acute injuries—*not* chronic disease pathologies—that should have prompted further analysis of the drug's potential nephrotoxic (*i.e.*, toxic to kidney function) capabilities. Throughout his report, he disagrees with other pathologists' animal-study findings of chronic kidney conditions. *See, e.g.*, Moeckel Report at 10 (2-year study, disputing finding of CPN, claiming to have found acute injuries, such as tubular injury and inflammatory filtrate), 11 (Fig. 2, same), 14 (Fig. 4, same), 21 (Fig. 7, one-year study, same), 25 (13-week study, image B, noting severe tubular injury), 26 (same study, deceased rats, asserting that the "kidney injury lesions . . . were not chronic but rather consistent with tubular injury due to drug toxicity"), 27 (different 13-week study, "the kidney tissue sections of the treated animals showed much more acute tubular

[2]While "death" was also selected on Plaintiff's operative short form complaint, that was clearly in error, as Plaintiff is still living.

injury (ATI) and acute interstitial nephritis (AIN) than described in the study reports"). Importantly, at no point in his report or deposition does Dr. Moeckel link his purported animal-study findings to the sole alleged injury in this case: drug-induced human CKD. Put differently, this Plaintiff does not allege the sort of acute kidney injuries (*e.g.*, tubular injury) detailed in Dr. Moeckel's Report.

Further indicative of the gap between his opinions and this case, consider Dr. Moeckel's deposition testimony. Dr. Moeckel, who claims to examine human renal tissues "[a]lmost every day," likens human CKD to rat CPN, noting that "progression of [CKD] . . . has many similar features of those described in CPN in the rat." Moeckel Dep. vol. II at 246:21–24. On the one hand, this view has been rejected by Plaintiff's *own* internal medicine expert, Professor Mehal, who admitted during his deposition that "chronic progressive nephropathy in rats is a unique thing to rats, so it wouldn't make sense to compare it to humans, because they don't get that particular disease." Ex. D, 7-14-2021 Dep. of Wajahat Mehal, Ph.D., M.D. ("Mehal Dep.") at 210:2–7. On the other, Dr. Moeckel admits that he has *never* seen CPN in rat kidneys. Moeckel Dep. vol. II at 348:3–4 ("I have never seen CPN in mice that I have loo ked at."). Nor does he recall if he has "ever diagnosed on a human renal biopsy CKD secondary to PPI use." *Id.* at 247:18–248:4. Further, he does not claim that the preclinical findings should have led to additional or different product warnings, nor that any such warnings could have impacted the healthcare provider's decision to prescribe PPIs in this case. Thus, whatever the relevance of his animal-study findings contesting the existence of chronic conditions in rat kidneys, and whether the manufacturer could have conducted more animal studies of acute renal injuries, those opinions simply do not fit in a case concerning human CKD.

Other courts applying the Rule 702 "fit" requirement have held that "where there is expert testimony that a given substance can cause a certain condition, but an exposed plaintiff complains of a different condition, the expert's opinion, even if reliable, does not fit the facts of the case, is not helpful to the trier of fact, and, thus, is inadmissible." *Amorgianos v. Nat'l R.R. Passenger Corp.*, 137 F. Supp. 2d 147, 163 (E.D.N.Y. 2001). Such is the case here.

C. Qualifications: Dr. Moeckel, Who Is Not a Veterinary Pathologist and Has No Formal Training in Rat Renal Pathology, Is Not Qualified to Critique Rat Pathology Opinions About a Rat-Specific Kidney Condition He Claims to Have Never Seen.

No doubt, Dr. Moeckel's credentials reflect that he is well-qualified as an anatomic pathologist with extensive experience in human kidneys. *See generally* Moeckel Report at 2–3 & Ex. A (CV). But his opinions in this case have *nothing* to do with the pathology of human kidneys. Instead, Dr. Moeckel examined images from Takeda's preclinical studies—comprised of tests of *inter alia* rat, mouse and dog kidneys—for the purpose of assessing a potential drug toxicity in animal kidneys that, by analogy, might support a potential drug toxicity in human kidneys. These opinions thus drift far beyond his area of specialized expertise. The point is not that he considered animal studies as a tool in predicting the reaction of human kidneys; it is that his opinions pertain entirely to animal studies, about a specific chronic rat condition that he claims to have never seen, and he willfully takes issue with published literature so that he may critique the original animal study findings—all without specialized training in veterinary pathology, and without knowing the training, qualifications, or methodology utilized by the original animal-study pathologists.

Dr. Moeckel admittedly is not a veterinary pathologist, toxicologist, or nephrologist, and he does not treat kidney disease. Moeckel Dep. vol. I at 33:3–19, 34:5–16, 42:5–6. He admits to not having formal training in mouse renal pathology. *See* Moeckel Dep. vol. II at 347:19–348:8. He has never testified before as an animal renal pathologist, about the "relationship between animal

histopathology and human disease," or "the types of opinions that are reflected in [his] report" in this case. Moeckel Dep. vol. I at 21:22–22:9. Nor has he consulted with pharmaceutical companies on the use of animal studies to obtain FDA approval of new drugs. *Id.* at 43–44. Most importantly, despite claiming to have reviewed "hundreds of mouse kidney sections," he concedes that he has *never* seen the primary rat-specific chronic condition, CPN, at the heart of his critique of the pathologists for Takeda's animal studies. Moeckel Dep. vol. II at 347:19–348:4; *accord* Moeckel Dep. vol. I at 179:20–21.

Yet, Dr. Moeckel's lack of specialized training in this niche area does not prevent him from blindly criticizing the pathologists who conducted Takeda's animal studies. Though he admittedly *does not know* whether the study pathologists were veterinary pathologists or had specialized experience diagnosing CPN, he nevertheless impugns their training and competence and claims superior knowledge to them. Moeckel Dep. vol. II at 347:10–348:22. He offers no basis for his superior qualifications; he simply assumes as much. His expert report similarly demonstrates a willingness to challenge other pathologists' training and competence without consideration of their qualifications. *See* Moeckel Report at 30 (noting "significant doubt that the tissues were reviewed by competent renal pathologists"). Name-calling aside, Dr. Moeckel provides no explanation for where the original pathologists opinions go wrong. *Id.* at 27–30.

A double-standard emerges when Dr. Moeckel considers the opinions of FDA pathologists, however. He acknowledges that Takeda submitted its animal studies for the FDA's review. Asked if the FDA reviewers reached the same conclusions as the Takeda animal studies, would he still disagree with the conclusions, Dr. Moeckel balked: "If I don't know the reviewer and I cannot evaluate what the expertise is of the reviewer, I would not know what I should think of the result." Moeckel Dep. vol. II at 404:14–22. (Never mind that the FDA, in its exclusive authority of

approving drugs for market, did not find similar faults in Takeda's animal studies or require additional testing of the nature suggested by Dr. Moeckel.)

Similar arrogance permeates Dr. Moeckel's treatment of published literature on rat kidney conditions and specifically CPN. Most troubling, given his peculiar rat-study-to-human-implications opinions here, he disagrees with authoritative literature showing limits on the ability to extrapolate potential human hazards from rat renal tissue. Yet again, he provides no rationale for this disagreement. Specifically, he recognizes that the Haschek and Rousseaux *Handbook on Toxicological Pathology* is a "well-recognized textbook in the field," Moeckel Dep. vol. I at 73:17–23, but takes issue with a passage from the treatise's chapter on kidneys:

> In the safety assessment of new molecular entities, the concordance in response to xenobiotics in rat and human strongly supports the rat as a good predictor for human renal hazard. The exceptions in concordance include two categories: Immune-mediated drug injury in humans and the xenobiotic-associated unique alpha2µ-globulin nephropathy syndrome in male rats.

Id. at 73–76; Ex. E, Excerpt from Haschek and Rousseaux *Handbook on Toxicological Pathology*. In other words, the treatise notes a lack of concordance—*i.e.*, symmetry—in human and rat responses such that rat kidneys are *not good predictors* for immune-mediated drug injury in humans. Without addressing the lack of concordance in human and rat response, Dr. Moeckel simply disagrees with the statement because he "believe[s] that drug-induced immune lesions . . . can be induced in rats—by drugs." *Id.* at 76:8–10. (He conceded not being familiar with the alpha2µ-globulin nephropathy syndrome.)

Later, he challenged Takeda's definition of CPN, stating his "belie[f] . . . that CPN cannot spontaneously occur in aging rats," and that "the molecular mechanisms underlying that process are not entirely clear." Moeckel Dep. vol. II at 411:12–19. But he repeatedly acknowledges that the literature discusses CPN as a spontaneous condition. *Id.* at 295:24–296:2, 297:9–19. As does

Plaintiff's own toxicology expert. *Cf.* Ex. F, 6-21-2021 Dep. of Martyn T. Smith, Ph.D. at 136:9–15 (agreeing that CPN is the "most commonly encountered spontaneous background finding in laboratory rodents"). And he further admits that there were "similar" lesions present in the renal tissue of control animals, *see id.* at 296–97, which, by definition, could not be drug-induced.

In sum, time and again, Dr. Moeckel's animal pathology opinions go beyond his qualifications as an experienced pathologist of human kidney disease. He glibly critiques other pathologists' competence and training, with no knowledge of either, and he disputes their opinions about a rat-specific chronic condition, CPN, that he claims to have never seen. Although the Rule 702 standard for qualifications is fairly deferential, recognizing that a "broad range of knowledge, skills, and training" may qualify an expert, *Schneider*, 320 F.3d at 404, it does require adequate specialized knowledge that is "specific to the matters [the expert] proposes to address." *In re Williams Sec. Litig.*, 496 F. Supp. 2d 1195, 1232 (N.D. Okla. 2007), *aff'd sub nom. In re Williams Sec. litigation-WCG Subclass*, 558 F.3d 1130 (10th Cir. 2009). "[M]erely possessing a medical degree is not sufficient to permit a physician to testify concerning *any* medical-related issue." *Ralston v. Smith & Nephew Richards, Inc.*, 275 F.3d 965, 970 (10th Cir. 2001). Dr. Moeckel's specialized training as a pathologist of human kidney tissue cannot bear the weight of his idiosyncratic and contrarian animal study opinions here, and thus his opinions should be excluded in their entirety.

D. Dr. Moeckel's Subjective, Idiosyncratic, Unverifiable, and Undocumented Review of Thousands of Slides Lacked Any Semblance of a Reliable Methodology.

Dr. Moeckel's opinions should also be excluded for lack of a reliable methodology. Methodological flaws permeate his analysis at almost every stage, from the undocumented image analysis to idiosyncratic definitions of CPN and inconsistent interpretations of data to form dose-dependency conclusions at odds with his own definition of dose dependency. These combined

flaws, along with his own testimony, confirm that Dr. Moeckel's opinions are conclusion driven and not the result of reliable scientific processes.

1. The Undocumented, Subjective Analysis of Thousands of Images of Renal Tissue Is Unverifiable, Unrepeatable, Open to Bias, and Unreliable.

Beginning with his examination of thousands of images of renal tissue from 15 Takeda preclinical studies, Dr. Moeckel's approach was highly subjective, undocumented, uncalibrated, and incapable of repetition. The following flaws riddled his analysis:

- lack of written notes about the thousands of slides he purportedly reviewed, Moeckel Dep. vol. II at 277:9–24;
- lack of a grading system to differentiate the severity of lesions and other cellular phenomena, Moeckel Dep. vol. I at 102:8–13;
- lack of incidence rates for lesions, by slide and test group, and lack of cross-references comparing his findings to the original studies' lesion-specific findings, *id.* at 103:4–17, 125:1–15;
- lack of tabulation regarding lesion results and failure to generate a dose-response curve, Moeckel Dep. vol. II at 312:11–13;
- lack of methodology for adjusting / comparing human dosage levels to the rat dosage levels in the animal studies, *see id.* at 258–62, 338, 343; and
- First time conducting such an analysis, for litigation, *see* Moeckel Dep. vol. I at 21:22–22:9.

His subjective, undocumented methodology also was not susceptible to peer review. Nevertheless, defense counsel gave Dr. Moeckel an opportunity to demonstrate his methodology and reassess some of the slides he purportedly examined, live, during the deposition. *Id.* at 382–392. Asked if he could identify anything remarkable about the slides' pathology, using a variety of degrees of resolution, Dr. Moeckel could not ascertain anything of significance, claiming poor image quality. *See id.* (But a veterinary pathologist deposed by Plaintiff in this litigation had no

such trouble identifying slides during his deposition. Ex. G, 9-8-2021 Dep. of John C. Seely, DVM at 164–73.)

Relying entirely on a subjective process and "mental notes," *id.* at 277:22–278:2, like this, is contrary to a reliable, scientific methodology, because it is unverifiable and unrepeatable. In other words, he does not "show his work," or walk through the steps of the analysis in any sort of disciplined manner; he just arrives at conclusions.

Courts have expressed skepticism of such undocumented, subjective slide-review processes precisely for this reason. For instance, in *In re Diet Drugs*, another federal court in this Circuit excluded slide-based animal pathology opinions with near identical flaws to the ones in Dr. Moeckel's analysis. MDL No. 1203, 2001 WL 454586 (E.D. Pa. Feb. 1, 2001). In that case, the plaintiff relied on Dr. Colin Bloor's pathological review of slides to determine the impact of certain diet drugs on rat hearts, as may be relevant to ascertaining a cardiotoxicity in human hearts. *See id.* at *4, 11. The court faulted Dr. Bloor's unblinded review of the slides, his lack of a documented grading system and peer review, and his inability to reproduce his own results when shown the same slides in blind conditions and asked to rescore them. *Id.* at *12–13. Without proper controls on the methodology, "the possibility of bias increases with the subjectivity of the analysis." *Id.* at *13.

The Third Circuit has prescribed a number of factors for determining the reliability of an expert's methodology:

> (1) whether a method consists of a testable hypothesis; (2) whether the method has been subjected to peer review; (3) the known or potential rate of error; (4) the existence and maintenance of standards controlling the technique's operation; (5) whether the method is generally accepted; (6) the relationship of the technique to methods which have been established to be reliable; (7) the qualifications of the expert witness testifying based on the methodology; and (8) the non-judicial uses to which the method has been put.

Oddi, 234 F.3d at 145 (citing *In re Paoli R.R. Yard PCB Litig.*, 35 F.3d 717, 742 n.8 (3d Cir. 1994) ("*Paoli II*")). *In re Diet Drugs* explained that Dr. Bloor's subjective, slide-based review failed many of these factors. Summarizing the expert's foibles, the court explained that "Dr. Bloor's semi-quantitative scoring methodology has not been demonstrated to have a known or potential rate of error, to be testable, or to have any control standards." *Id.* at *12. These specific flaws overcame the fact that it was commonplace for pathologists to generally employ some form of subjective review of histological slides in rendering opinions. *Id.* at *14 (discounting general acceptance, against numerous flaws).

So too here. Dr. Moeckel did not even attempt the "semi-quantitative scoring methodology" deemed insufficient in *In re Diet Drugs*. The myriad flaws in Dr. Moeckel's undocumented, subjective, slide-based review of Takeda's animal studies depart from most if not all signposts of a reliable methodology, and thus render his opinions inadmissible.

Finally, the *In re Diet Drugs* court rejected Dr. Bloor's unexplained extrapolation from the animal slides to findings about cardiotoxicities in humans. *Id.* at *15 (citing *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 144 (1997), which affirmed the exclusion of experts' opinions on causation in humans because plaintiff never explained how and why experts could extrapolate their opinions from animal studies far removed from circumstances of plaintiff's exposure). Other courts have similarly expressed concerns about such extrapolations without a reasonable scientific explanation. *E.g.*, *Hall v. Baxter Healthcare Corp.*, 947 F. Supp. 1387, 1410 (D. Or. 1996) (citations omitted) (collecting authority recognizing that "[e]xtrapolations of animal studies to human beings are generally not considered reliable in the absence of a scientific explanation of why such extrapolation is warranted"). The same deficiency undercuts Dr. Moeckel's analysis here. As noted above, Dr. Moeckel summarily rejected the Haschek and Rousseaux treatise, which

noted limits in the ability to extrapolate certain kidney reactions in rats to humans. *See supra* Part III.C. Such contrary opinions exceed Dr. Moeckel's qualifications, and he offers no reliable scientific basis for charting his own path on this topic.

2. Dr. Moeckel's Dose-Dependency Opinions Rest on Interpretations of Others' Pathology Data, and His Findings Depart from the Data and His Own Definition of Dose-Dependency.

The logic leaps continue with Dr. Moeckel's dose-dependency conclusions, which contradict his own definition of dose-dependency and common sense. Typically, when there is a dose-dependent relationship, an adverse reaction would become more severe when dosage increases—for instance, mild lesions at a low dosage rate might become larger, severe lesions at a higher dose. Put differently, the term encompasses the severity of reactions, not just frequency. Dr. Moeckel acknowledges as much: "if I see in a study that a *certain type of injury is exacerbated with increase in dosage*, . . . I think that is an important signal." Moeckel Dep. vol. I at 161:4–7 (emphasis added). In other words, "it's the severity of the lesion . . . in the increasing dose group." Moeckel Dep. vol. II at 331:18–21. But Dr. Moeckel's actual dose-dependency opinions appear to track frequency of lesions—and even then, he highlights certain modest increases as significant and completely disregards decreases in frequency and severity that cut against his findings.

For instance, Dr. Moeckel emphasized his disagreement with the original findings of Report A-29-1977/TA91-024, focusing on a table that appeared in that report, which he reproduced at page 9 of his report.

Table 5.3.2-11

INCIDENCE OF CHRONIC PROGRESSIVE NEPHROPATHY DOS AND TS - FEMALES

Dosage	Vehicle Control A		5 mg/kg		25 mg/kg		75 mg/kg		150 mg/kg	
	DOS	TS	DOS	TS	DOS	TS	DOS	TS	DOS	TS
Number Examined	46	24	27	43	42	28	31	39	28	42
CHRONIC PROGRESSIVE NEPHROPATHY										
- trace	9	8	6	17	9	13	4	10	4	9
- mild	14	4	8	9	22	11	17	22	17	26
- moderate	2	3	2	2	2	1	2	5	4	7
- severe	2	2	2		2		4	1		
TOTAL	27	17	18	28	35	25	27	38	25	42

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Moeckel Report at 9 (citing A-29-1977/TA91-024 Table 5.3.2-11). To see where the logic in his opinions breaks down, all frequently refer to the lesion data in the above table by combining the figures in the "DOS" and "TS" columns for each dose level. (Hence, 6+17=23 "trace" lesions observed at the 5 mg/kg dose level.) Notably, this particular criticism from Dr. Moeckel goes to the *interpretation of the data*, not the pathological assessment of the slides—because, again, Dr. Moeckel did not use a grading system, but rather the eyeball test.

The report's original findings sensibly pointed to the complete lack of "severe" CPN in the highest dosage group (150 mg/kg) as reason to doubt that the drug "caused a direct effect on the kidneys." *Id.* at 9 (quoting Dr. Levin). Though he does not disagree with the numbers (or the test samples they represent), Dr. Moeckel rejects the report's reasonable interpretation and discards the lack of severe lesions as an "outlier." *Id.* at 303:19. He also ignores decreases in frequency of other degrees of lesions, as dosage increases, so long as some purported increase in frequency that will support his narrative. *See id.* at 300–04. To see his inconsistent treatment of this data, consider:

Lesion Severity	**Change in Frequency by Dosage[3]**	**Dr. Moeckel's Treatment**
Trace	Decreases from high of 23 at low dosage (5 mg/kg), at each dosage increase, to low of 13 at highest dosage (150 mg/kg), which was lower than control group count of 17	*Ignored decreasing frequency with dosage.
Mild	Control group and low dose (5 mg/kg) show 18 and 17 mild lesions, then medium and high dose show 33, 39, and 43 mild lesions, respectively	*Highlights increasing frequency of mild lesions at medium dose, discounts plateau of frequency at highest dose
Moderate	Varies from 5 moderate lesions in control group, 4 and 3 in lower doses (5 and 25 mg/kg, respectively), and 7 and 11 in higher doses (75 and 150 mg/kg respectively)	*Highlights increase from 7 to 11 (+4) as a "significant increase," ignoring contrary variance in lower doses.
Severe	Varies from 4 severe lesions in control group, to between 2–5 lesions at increasing dosage (5 mg/kg–75 mg/kg), to 0 severe lesions at highest dosage (150 mg/kg)	* Discarded decrease from 5 to 0 (-5) as "outlier." *Id.* at 303:19. *suggests anomaly could be explained as "spontaneously occurring lesion," *id.* at 301:18–20, despite repeatedly denying the presence of spontaneous lesions in the slides he reviewed

In other words, if there was an increasing number with increased dosage, it was significant, but a decreasing number was an outlier, and it mattered not whether increasing dosage produced more *severe* lesions—contrary to common sense and Dr. Moeckel's own definition of dose-dependency. That is not a reliable scientific methodology; it is self-fulfilling prophecy and *ipse*

[3]For purposes of interpreting the table, the defense combines the data from the "DOS" and the "TS" columns.

dixit. *See Joiner*, 522 U.S. at 147 ("[N]othing in either *Daubert* or the Federal Rules of Evidence requires a district court to admit opinion evidence that is connected to existing data only by the *ipse dixit* of the expert.").

3. Dr. Moeckel's Idiosyncratic Definition of CPN Is at Odds with Leading Authority and Reflects His Desire Not to Let Manufacturers "Off the Hook."

Then there was Dr. Moeckel's peculiar definition of CPN, the chronic rat condition he admits never having seen. He cites a 2012 article by Frazier and Seely, produced as part of the International Harmonization of Nomenclature and Diagnostic Criteria for Lesions in Rats in Mice, as a source he relied upon to educate himself on CPN, Moeckel Dep. vol. I at 111:17–20, but disagrees with numerous portions of its consensus findings, including its discussion of early stages of CPN in young rats, *id.* at 118–123. Dr. Moeckel rejects the notion that basophilic tubule or regeneration in the outer kidney can be the first signs of CPN in young adult rats, as reported in that article, because "I don't think that a young adult rat should have CPN." *Id.* at 123:15–20.

Pressed for an explanation for his reticence, Dr. Moeckel expressed concerns about the medical definition of CPN becoming an all-encompassing "wastebasket" that concealed the negative effects of drugs and let manufacturers "off the hook." *Id.* at 120:8–18. He pointed to no literature rejecting the Frazier and Seely article's characterization of CPN, including its finding that basophilic tubule and outer kidney regeneration can be early signs of CPN in young adult rats; merely his *belief* that rats needed to be 18 months or older to develop the condition that, again, he has never seen or studied prior to this litigation. So quick was he to disagree with the Frazier and Seely article's consensus definition of CPN that he even rejected its conclusion that CPN was "spontaneous in origin and of unknown etiology," *id.* at 123:3–7, despite otherwise admitting the spontaneous nature of CPN, *see, e.g.*, Moeckel Dep. vol. II at 295:24–296:2.

Dr. Moeckel's dismissiveness towards the Frazier and Seely article resembles his attitude towards the Haschek and Rousseaux treatise, which noted limitations in extrapolating rat kidney conditions onto human kidney reactions, as well as his rejection of the Takeda animal study findings without ascertaining the methodology or training of the original pathologists. *See supra* Part III.C.[4] Dr. Moeckel admitted he would not second-guess the FDA reviewers of the same animal studies without knowing their training and reasons, but extends no such courtesy to this literature or the pathologists from the Takeda animal studies.

At the same time that he readily narrows the scope of CPN, while amplifying any possible sign of a drug-induced link between PPIs and renal lesions, he admits that the biological mechanism by which PPIs allegedly cause renal lesions remains unknown. Moeckel Dep. vol. II at 316:12–15 ("[T]he molecular mechanism of how PPIs injure the tubular epithelial cell are still enigmatic, in my opinion."). So he does not know how alleged PPI-induced lesions occur, and he saw similar lesions in the control groups of rats not exposed to PPIs, but he is *certain* that there must be a link. That is a conclusion-driven opinion, not a data-driven opinion.

Mere conjecture that CPN cannot exist in young rats *because* otherwise drug manufacturers are "off the hook," by a person who is not a veterinary pathologist, has no special training on diagnosing rat kidneys, and has never seen CPN, is not a reliable scientific methodology. His opinions should therefore be excluded in their entirety.

IV. CONCLUSION

Speculation and unrecorded conclusion-driven analysis plague Dr. Moeckel's animal pathology opinions in this case, which drift far from his qualifications, unmoored from the

[4]This finding aligns with the opinion of Plaintiff's internal medicine expert that CPN "is a unique thing to rats, so it wouldn't make sense to compare it to humans. Mehal Dep. at 210:2–7.

guideposts of a reliable methodology. He admittedly is not an animal pathologist, but that is what he offers here: opinions about the conditions of rat and dog kidneys, solely for the purpose of critiquing the original studies' findings. He offers no scientific basis for disagreeing with the published literature on the chronic kidney conditions affecting rats that he concedes he has never seen. Notably, he did not keep any records or notes of the slides he reviewed, nor did he apply any sort of grading system to ascertain the severity of a particular kidney phenomenon in a given slide. Further, the slides he reviewed told him which slides belonged to the control group. This lack of objectivity, discipline, and precision not only defies basic scientific principles, but insulates Dr. Moeckel's opinions from meaningful review.

This Court should therefore grant Takeda's Motion to Exclude and bar Dr. Moeckel's opinions consistent with the *Daubert* standard and Federal Rule of Evidence 702.

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Respectfully submitted,

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